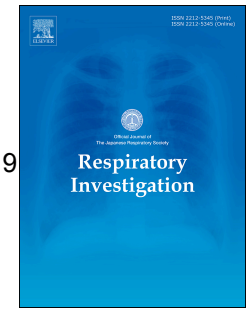
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.



Patient-centered outcomes at hospital discharge in mechanically ventilated COVID-19 patients in Kobe, Japan: A single-center retrospective cohort study

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PII: S2212-5345(22)00091-0

DOI: https://doi.org/10.1016/j.resinv.2022.06.010

Reference: RESINV 788

To appear in: *Respiratory Investigation*

Received Date: 7 September 2021

Revised Date: 31 May 2022

Accepted Date: 21 June 2022

Please cite this article as: Ito J, Kawakami D, Seo R, Iwata K, Ouchi K, Nonami S, Miyoshi Y, Tatebe M, Tsuchida T, Asaka Y, Takeda C, Nishihara H, Mima H, Doi A, Tomii K, Ariyoshi K, Patient-centered outcomes at hospital discharge in mechanically ventilated COVID-19 patients in Kobe, Japan: A single-center retrospective cohort study, *Respiratory Investigation*, https://doi.org/10.1016/j.resinv.2022.06.010.

Title: Patient-centered outcomes at hospital discharge in mechanically ventilated COVID-19 patients in Kobe, Japan: A single-center retrospective cohort study

Word counts:

Abstract: 246 words

Manuscript: 3,484 words

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Abstract

Background: Apart from saving the lives of coronavirus disease (COVID-19) patients on mechanical ventilation (MV), recovery from the sequelae of prolonged MV (PMV) is an emerging issue.

Methods: We conducted a retrospective study among consecutive adult COVID-19 patients admitted to an intensive care unit (ICU) in Kobe, Japan, between March 3, 2020, and January 31, 2021, and received invasive MV. Clinical outcomes included in-hospital mortality and recovery from COVID-19 in survivors regarding organ dysfunction, respiratory symptoms, and functional status at discharge. We compared survivors' outcomes with MV durations of >14 days and ≤14 days.

Results: We included 85 patients with a median age of 69 years (interquartile range, 64–75 years); 76 (89%) patients had at least 1 comorbidity, 72 (85%) were non-frail, and 79 (93%) were functionally independent before COVID-19 infection. Eighteen patients (21%) died during hospitalization. At discharge, 59/67 survivors (88%) no longer required respiratory support, 50 (75%) complained of dyspnea, and 40 (60%) were functionally independent. Of the survivors, 23 patients receiving MV for >14 days had a worse recovery from COVID-19 at discharge compared with those on MV for ≤14 days,

as observed using the Barthel index (median: 35 [5-65] vs. 100 [85-100]), ICU mobility scale (8 [5-9] vs. 10 [10-10]), and functional oral intake scale (3 [1-7] vs. 7 [7-7]) ($P <$ 0.0001).

Conclusion: Although four-fifths of the patients survived and >50% of survivors demonstrated clinically important recovery in organ function and functional status during hospitalization, PMV was related to poor recovery from COVID-19 at discharge.

Keywords

activities of daily living; COVID-19; critical care; Japan; mechanical ventilation

Abbreviations

ADL: activities of daily living, APACHE II: Acute Physiology and Chronic Health Evaluation II, BI: Barthel index, BMI: body mass index, CCI: Charlson comorbidity index, CFS: clinical frailty scale, FiO_2: fraction of inspired oxygen, HADS: Hospital Anxiety and Depression Scale, HR: hazard ratio, ICU: intensive care unit, KCGH: Kobe City Medical Center General Hospital, MMSE: Mini-Mental State Examination, MRC: Medical Research Council, PaO_2: partial pressure of arterial oxygen, PMV: prolonged mechanical ventilation, QOL: quality of life, SARS-CoV-2: severe acute respiratory

syndrome coronavirus 2, SOFA: sequential organ failure assessment, CI: confidence interval

1. Introduction

The clinical spectrum of coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), ranges from mild to critical. Most patients are asymptomatic or have mild disease, while some patients (5%) develop critical illness [1]. Although mortality in critically ill patients with COVID-19 has been reported to improve over time, it continues to remain high [2,3]. Additionally, prolonged mechanical ventilation (PMV) has been reported to lead to the development of physical, cognitive, and mental health problems in non-COVID-19 critical illness survivors following discharge from the intensive care unit (ICU) [4-6]. Recently, the international multistakeholder working group proposed patient-centered outcomes including mortality, respiratory failure, multiorgan failure, shortness of breath, and recovery, based on a survey of COVID-19 patients, their family members, members of the general public, and health professionals from 111 countries [7,8]. To date, most clinical studies on critically ill COVID-19 patients have focused on mortality as the primary outcome [9-13], while there has been a paucity of literature clarifying organ dysfunction, prolonged symptoms, functional status, and quality of life (QOL) of survivors [14-19]. Furthermore, only a few studies have examined the impact of the mechanical ventilation (MV) period on these outcomes, and the outcomes evaluated in those studies are also limited [18,19]. Our

primary objective was to report comprehensive patient-centered outcomes at hospital discharge for COVID-19 patients following invasive MV. Our secondary objective was to determine the relationship between the patient-centered outcomes and the duration of MV in survivors.

2 Methods

2.1. Study design

This single-center, retrospective, observational study was conducted at Kobe City Medical Center General Hospital (KCGH), a 768-bed tertiary referral center providing emergency medical care to approximately 35,000 patients per year in Kobe, Japan. In Kobe, the first case of COVID-19 was reported on March 3, 2020, and as of January 31, 2021, a total of 5,518 cases had been reported. Of the 1,962 new COVID-19-positive cases in the city between January 1 and January 28, 2021, 677 (34.5%) were tested for the presence of the N501Y mutation, and no mutated strains were found [20]. As of January 13, 2021, the city had reserved a maximum of 39 beds for severe or critically ill COVID-19 patients; 36/39 beds were within KCGH. Thus, most of the mechanically ventilated COVID-19 patients in the city were preferentially admitted or transferred to

KCGH. Our surge capacity strategies and patient management during the first 3 months of the city's COVID-19 outbreak have been described in our previous study [21]. Our patient management during the study period was generally based on the guidelines in place at the time. The COVID-19 rehabilitation team consisted of two physical therapists experienced in providing early and structured rehabilitation for mechanically ventilated patients with non-COVID-19 illnesses. The physical therapists were responsible for optimizing airway clearance and rib cage elasticity and for deciding the initiation and progression of early mobilization. All COVID-19 inpatients were assessed by the physical therapists at admission. Among the patients, those on MV or high-flow nasal cannula were considered the highest priority for rehabilitation. Rehabilitation was planned every day on weekdays, except before and within 24 h after endotracheal intubation, before and immediately after extubation or tracheostomy, and respiratory deterioration, such as a sudden increase in inspiratory oxygen level. Usual care was provided on the holidays, including postural drainage by nurses.

2.2. Study population

This study included consecutive adult patients aged ≥18 years with laboratory-confirmed COVID-19 admitted to a COVID-19-dedicated ICU at the KCGH between March 3, 2020, and January 31, 2021, and on invasive MV support. Laboratory confirmation of COVID-19 was based on RNA detection of SARS-CoV-2 using reverse transcription-polymerase chain reaction analysis of nasopharyngeal swab specimens. Patients were observed at follow-up sessions until hospital discharge, death, or May 13, 2021, whichever occurred first.

Our local Institutional Review Board approved the study (approval number: zn210623) and waived the requirement for written informed consent. Our study adhered to the Strengthening of Reporting of Observational Studies in Epidemiology reporting guidelines [22].

2.3. Data collection

Using electronic medical records, we collected patients' data on age, sex, race, body mass index (BMI), smoking history, comorbidities, infection route, symptom onset, and presenting symptoms before hospital admission, and laboratory and imaging tests on ICU admission. Data on the Charlson comorbidity index (CCI), clinical frailty scale (CFS),

and Barthel index (BI) were used to evaluate comorbidities, frailty status, and performance in activities of daily living (ADL) before COVID-19 onset, respectively [23-25]. Sequential organ failure assessment (SOFA) score, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, and ratio of the partial pressure of arterial oxygen (PaO_2) to the fraction of inspired oxygen (FiO_2) at ICU admission were used to evaluate disease severity [26,27]. Diagnoses of acute respiratory distress syndrome and sepsis were made based on the Berlin definition and Sepsis-3, respectively [28,29]. We also reviewed the treatments administered in the ICU, including respiratory support (high-flow nasal cannula oxygen therapy, noninvasive ventilation) before MV and neuromuscular blockade use, except during the intubation procedure, prone positioning, venovenous extracorporeal membrane oxygenation, tracheostomy, catecholamine use, renal replacement therapy, nutritional therapy, therapeutic anticoagulation, and COVID-19-specific pharmacotherapies.

The general clinical outcomes included mortality, dispositions of the survivors at hospital discharge, duration of ICU and in-hospital stays, and duration of MV. To evaluate recovery from COVID-19 at hospital discharge in survivors, we used the following comprehensive assessment performed by treating physicians, nurses, or physiotherapists: organ dysfunction, patient-reported respiratory symptoms, functional status, and QOL.

BI was used for evaluating ADL at hospital discharge; ICU mobility scale for mobility status [30]; functional oral intake scale for oral feeding function [31]; Medical Research Council (MRC) score for muscle weakness [32]; Hospital Anxiety and Depression Scale (HADS) for psychological function [33]; Mini-Cog and/or Mini-Mental State Examination (MMSE) for cognitive function [34,35]; and EuroQol five-dimensional questionnaire for QOL [36]. The scales used in the present study and their interpretations are presented in Supplementary Table 1.

2.4. Statistical analysis

The statistical sample size was not calculated a priori owing to the nature of the study. Data of continuous and categorical variables are presented as median (interquartile range) and n (%), respectively. To determine the relationship between the duration of MV and the clinical outcomes in survivors, we compared the outcomes between PMV and non-PMV cohorts. PMV was defined as MV duration >14 days [37]. The Mann-Whitney U test and Pearson's chi-square test were used to examine the differences in continuous and categorical variables between the cohorts, respectively. Kaplan-Meier curves were constructed, and the log-rank test was used to compare recovery from COVID-19

regarding mobility status and oral feeding function after liberation from MV between the two cohorts. Cox proportional hazards models were also used to compare the outcomes over time, and the results were reported as hazard ratios (HRs) with 95% confidence intervals (CIs). Candidate variables considered for statistical analysis were determined based on those published in previous reports, as follows: age, sex, CCI, BI, and CFS prior to COVID-19 illness, SOFA score at ICU admission, neuromuscular blockade use, and systemic glucocorticoids use [5,6]. Due to the small number of events in this study, we performed univariate and not multivariate analyses to avoid overfitting in the model. A p-value of 0.05 was considered to be statistically significant. All data were analyzed using JMP 15 software (SAS Institute, Cary, NC, USA).

3. Results

3.1. Characteristics of the study population

Of the 5,518 patients with laboratory-confirmed COVID-19 in Kobe, 483 were admitted to KCGH between March 3, 2020, and January 31, 2021, of which 85 treated with MV were included in this study and observed at follow-up sessions until hospital discharge or death. All patients were Asian adults with a median age of 69 years (range: 64-75 years);

67 (79%) were men, and 62 (73%) had a history of smoking (Table 1). The median BMI of 79 patients was 24.6 (range: 22.2-26.8) kg/m^2. Seventy-six (89%) patients had at least one comorbidity; the most common comorbidities were hypertension (52 [61%]), diabetes (32 [38%]), chronic lung disease (18 [21%]), and cardiovascular disease (17 [20%]). The median CCI score was 3 (range: 2-4). Before COVID-19 onset, 72 (85%) patients were classified as non-frail and 79 (93%) were functionally independent. All patients met the criteria for both acute respiratory distress syndrome and sepsis at the time of ICU admission (Supplementary Table 3). The median SOFA and APACHE II scores during the first 24 h after ICU admission were 6 (range: 4-9) and 18 (range: 15-23), respectively. The median PaO_2/FiO_2 ratio on ICU admission was 112 (range: 85-154). Treatments administered throughout the ICU stay are summarized in Supplementary Table 4. During MV, 31 (36%) patients received neuromuscular blockade, and 19 (22%) were placed in the prone position. None met the predetermined criteria for the initiation of venovenous extracorporeal membrane oxygenation or were treated with it. Tracheostomy was performed in 21 patients (25%).

3.2. Clinical outcomes at hospital discharge

As of May 13, 2021, 18 (21%) patients died in the hospital with a median duration of hospital stay of 32 (range: 13-43) days; 11 (13%) died in the ICU and 7 (8%) died in the step-down wards after ICU discharge. The causes of death were multiorgan dysfunction (n = 10), respiratory failure (n = 6), and respiratory and cardiovascular failure (n = 2).

Of the 67 survivors, 35 were discharged home and 32 were transferred to another hospital (Table 2). The median duration of ICU and hospital stays were 14 (range: 9-29) and 27 (range: 17-53) days, respectively. The median duration of MV and hospital stays after liberation from MV were 9 (range: 5-22) and 17 (range: 10-36) days, respectively. Organ dysfunction, patient-reported respiratory symptoms, and recovery from COVID-19 at hospital discharge in 67 survivors are summarized in Tables 3 and 4. The median SOFA score at hospital discharge was 1 (range: 0-2). Fifty-nine (88%) patients no longer required respiratory support for a median of 9 days (range: 6-22 days) after liberation from MV. Of the 17 (25%) tracheostomized patients, all but one was liberated from MV. One patient with chronic kidney disease required new renal replacement therapy during hospitalization and until hospital discharge. The respiratory symptoms reported by the patients at hospital discharge were dyspnea on exertion (50 [75%]), cough (4 [6%]), and dyspnea at rest (1 [1%]); none of the patients complained of chest pain. By hospital discharge, 40 (60%) patients recovered to be functionally independent; 57 (85%) and 54

(81%) achieved independent walking and total oral intake at a median of 8 days (range: 5-30 days) and 4 days (range: 2-30 days) after liberation from MV, respectively. Comparisons of demographic features, clinical characteristics on ICU admission, and ICU treatments between the survivors with recovered ADL and those with impaired ADL are presented in Supplementary Tables 5–7. Of the 64 patients assessed by the MRC score, muscle weakness was observed in 18 (28%). Of the 54 patients assessed by HADS, anxiety and depression were observed in 18 (33%) and 17 (31%) patients, respectively. In 55 patients assessed by the Mini-Cog and/or MMSE, 13 (24%) had cognitive impairment. The QOL of 57 patients assessed using the EuroQol five-dimensional questionnaire is shown in Figure 1. Overall, 27/57 (47%), 24/57 (42%), 27/57 (47%), 16/57 (34%), and 13/57 (23%) patients reported moderate, severe, or extreme problems in five dimensions, namely, mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, respectively.

3.4. Comparison of clinical outcomes between PMV and non-PMV cohorts

Of the 67 survivors, 23 (34%) were mechanically ventilated for >14 days (PMV cohort) and 44 (66%) were liberated from MV within 14 days (non-PMV cohort). Comparisons

of demographic features, clinical characteristics on ICU admission, and treatments in the ICU between the cohorts are presented in Supplementary Tables 8-10. The median duration of hospital stay after liberation from MV was 13 (range: 9-21) days and 36 (range: 27-53) days, respectively (Table 2). At hospital discharge, significantly fewer patients were discharged directly to home in the PMV cohort compared with the non-PMV cohort; recovery from respiratory failure, dyspnea, ADL, mobility status, oral feeding function, muscle strength, and psychological function was also significantly slower in the PMV cohort (Table 3 and 4). In the evaluation of 32 patients transferred to other hospitals, the duration of hospital stay after liberation from MV was longer in the PMV cohort than in the non-PMV cohort, but more patients in the PMV cohort required respiratory support, and dependent on ADL, mobility status, and oral feeding function at hospital discharge (Supplementary Table 11 and 12). Figure 2 shows the cumulative incidence of regaining independent walking and total oral intake over 60 days after liberation from MV in the PMV and non-PMV cohorts. The PMV cohort required significantly more time to regain independent walking (HR, 0.27; 95% CI, 0.15-0.50; P <0.0001) and total oral intake (HR: 0.04, 95% CI: 0.01-0.13, P <0.0001) after liberation from MV than the non-PMV cohort.

4. Discussion

In this study, we reported the patient-centered outcomes of 85 mechanically ventilated COVID-19 patients at hospital discharge. Most of the patients in the study population were aged >60 years and had underlying medical conditions but were not frail or functionally dependent before COVID-19 onset. At hospital discharge, four-fifths of the patients survived; most of the survivors no longer required organ support, and >50% of them recovered to be functionally independent. One-third of the survivors had been on MV for >14 days; they had poor recovery from COVID-19 at hospital discharge and required more days to regain their functional status after liberation from MV than those on MV for a shorter duration.

The patients in the study population were predominantly elderly men with some underlying medical conditions, a finding that is consistent with those reported in a meta-analysis of COVID-19 patients admitted to ICUs [9]. Noteworthily, despite having older age and comorbidities, most of our patients were non-frail and functionally independent before COVID-19 onset. An international multicenter study that included 5,711 hospitalized COVID-19 patients with a median age of 74 years, wherein 87% of whom did not require critical care admission, reported that patients classified as non-frail (CFS score of <3) were as low as 36% [38]. However, a European multicenter study, which

focused on critically ill patients, including 4,244 COVID-19 patients with a median age of 63 years, wherein 80% of whom received MV, reported a median CFS score of 2 (range: 2-3) [39]. A Japanese observational study that included 31 mechanically ventilated COVID-19 patients reported a median BI of 100, a finding similar to that observed in our study [19]. A possible explanation for the paradoxical low prevalence of frailty and functional dependency in mechanically ventilated COVID-19 patients is that patients with impaired ADLs and their family members may have been unwilling to receive MV [40]. Estimation of frailty and functional status before COVID-19 onset in critically ill patients requiring MV should be determined by the cohort that includes not only intubated patients but also those with do-not-intubate orders.

A Japanese nationwide multicenter registry study, which included 1,555 mechanically ventilated COVID-19 patients registered between January 1, 2020, and February 28, 2021, from 925 participating hospitals throughout Japan, reported in-hospital mortality of 26% [41]. Given the equivalent study period and patient backgrounds, such as age, sex, and underlying diseases, in our and the aforementioned study, the in-hospital mortality of 21% in our study would be comparable to that study.

In our assessment of organ dysfunction at hospital discharge, the median SOFA score was 1, and most of the patients were free from organ support. In previous studies reporting

respiratory failure at hospital discharge in COVID-19 patients supported by MV, approximately 50% of the patients required supplemental oxygen therapy at discharge [18,41]. Although it is difficult to simply compare the studies for the recovery from respiratory failure owing to variation in the timing of assessment, the novelty in our findings is that most survivors recovered to be free from supplemental oxygen therapy within a few weeks after liberation from MV.

The most common patient-reported respiratory symptom at hospital discharge was dyspnea on exertion. In a French study evaluating the post-COVID-19 condition using a telephone interview, one-third of 73 patients who received MV still complained of dyspnea at 4 months after hospital discharge [42]. Regardless of recovery from respiratory failure, persistent dyspnea at hospital discharge and afterwards would hamper the recovery of functional status and QOL of survivors.

In our assessment of functional status at hospital discharge, most patients recovered to independence in general ADL, mobility status, and oral feeding function, in line with the previous studies. A single-center study that included 109 survivors of mechanically ventilated COVID-19 patients in the United Kingdom reported that 83% were able to walk independently at hospital discharge [43]. A multicenter study that was conducted in the Republic of Ireland included COVID-19 patients who were treated with MV and

referred to speech and language therapy. The results showed that >90% of patients achieved total oral intake without tube feeding at hospital discharge [44]. Importantly, our findings imply that the mechanically ventilated COVID-19 survivors have the potential for short-term recovery in organ dysfunction and functional status despite being among the most severely ill on the COVID-19 spectrum. As a caveat, QOL assessment revealed that nearly half of the survivors had moderate-to-extreme problems in mobility, self-care, and usual activities and were transferred to post-acute care hospitals; considering their functional status before COVID-19 onset, the recoveries at hospital discharge demonstrated in our study are still not satisfactory for patients.

Our subgroup analysis of survivors showed that PMV was significantly associated with lower levels of COVID-19 recovery at hospital discharge and a longer time to regain functional status. These findings are consistent with those of previous studies of mechanically ventilated patients with and without COVID-19. Moreover, PMV, prolonged ICU stays and bed rest, and the use of neuromuscular blocking agents were found to result in muscle weakness and increase the risk of reduced functional status [4-6,18,19]. To enhance recovery from COVID-19, comprehensive evaluation of functional status and QOL and multidisciplinary rehabilitation interventions are essential, especially in patients with PMV. Furthermore, amidst the ongoing epidemic, it is important to

collaborate with local hospitals to provide seamless rehabilitation during the post-acute phase.

The present study has strengths worth noting. First, although this is a single-center study, it includes the majority of mechanically ventilated COVID-19 patients for approximately 1 year from a city with a population of 1.5 million. Second, we evaluated comprehensive patient outcomes at hospital discharge. Third, we focused on the duration of MV as a prognostic factor, which is simple, understandable, and easy to measure. Fourth, we documented patient recovery in terms of functional status after liberation from MV, using the Kaplan-Meier method, which enables comparison of the outcomes between studies with different time frames of evaluation. Finally, our findings will help COVID-19 patients requiring MV and their medical staff and family members to determine their treatment goals and treatment plan during acute and post-acute phases. Additionally, the findings will help policymakers to determine the potential need for healthcare capacity in post-acute care facilities.

The present study also has some limitations. First, consecutive mechanically ventilated COVID-19 patients were included during the study period; however, the sample size was small. Second, owing to the retrospective design, there were missing data and potential for measurement bias. Third, there was possible selection bias due to how decisions

regarding the use of MV were made; patients with impaired ADLs and their families may have been unwilling to receive MV, which may have affected the patient background, leading to an overestimation of clinical outcomes in this study. Furthermore, data availability for anxiety and depression, cognitive function, and QOL at hospital discharge was low at around 80%, which may have been due to patients' medical conditions and omissions in assessment by the medical staff. Thus, our findings, especially those regarding the patient's ADLs before COVID-19 onset and the recovery from COVID-19, should be interpreted with caution. Fourth, although we observed all patients until discharge or death through follow-up, the duration of hospital stay among survivors varied not only because of the patient's medical condition but also because of the availability of post-acute care hospitals at the destination. Moreover, long-term outcomes were not evaluated. Fifth, many confounding factors could not be eliminated, and the associations between the duration of MV and recovery from COVID-19 do not allow us to simply conclude that there are causal relationships. Finally, inhibitors of generalizability include racial differences, variant COVID-19 strains, and local COVID-19 prevalence and surge capacity. Furthermore, this study was conducted at a single institution, and our treatment strategy was modified according to the latest guidelines at

the time. Therefore, variations in hospital structures and processes also limit generalizability.

5. Conclusions

Although four-fifths of the patients survived and >50% of the survivors demonstrated clinically important recovery in organ function and functional status during hospitalization, PMV was associated with poor recovery from COVID-19 at hospital discharge. These findings may support COVID-19 patients, their family members, and healthcare providers in making decisions during the initiation and prolonged course of MV.

Acknowledgements

We would like to thank Editage (www.editage.com) for English language editing.

Authors' contributions

JI, DK, RS, KI, and CT conceptualized the study. JI, KI, KO, SN, YM, MT, TT, and HN contributed to data collection. JI performed data cleaning and statistical analysis, prepared the figures and drafted the manuscript. All authors contributed to data interpretation, revised the manuscript for important intellectual content, and approved the final version of the manuscript.

Conflicts of interest

KT received honoraria from AstraZeneca, Boehringer Ingelheim, Eli Lilly, and GlaxoSmithKline. All other authors have no conflicts of interest to declare.

Funding

This work was supported by the Ministry of Health, Labour and Welfare Research Program on the Intractable Respiratory Diseases and Pulmonary Hypertension Research Group (Grant Number JPMH20FC1027) for the preparation of the article.

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Figure legends

Figure 1. Quality of life (QOL) of 57 patients assessed using the EuroQol five-dimensional questionnaire at hospital discharge

Figure 2. Kaplan-Meier curves of functional status recovery in survivors

A) Independent walking was defined as a score of ≥9 on the intensive care unit mobility scale. The median time to regain independent walking after liberation from mechanical ventilation (MV) was 35 days in the prolonged MV (PMV) cohort compared to 6 days in the non-PMV cohort. B) Total oral intake was defined as a score of ≥4 on the functional oral intake scale. The median time to regain oral feeding function without tube feeding after liberation from MV was not reached in the PMV cohort compared to 3 days in the non-PMV cohort.

Table 1 Demographics of the study population

	Overall (n = 85)	**Survivors (n = 67)**	**Non-survivors (n = 18)**
Age, years	69 (64-75)	68 (62-73)	75 (67-82)
40-49	5 (6)	5 (7)	0
50-59	10 (12)	8 (12)	2 (11)
60-69	28 (33)	24 (36)	4 (22)
70-79	31 (36)	25 (37)	6 (33)
80-89	11 (13)	5 (7)	6 (33)
Sex			
Female	18 (21)	13 (19)	5 (28)
Male	67 (79)	54 (81)	13 (72)
Body mass index, kg/m^2	24.6 (22.2-26.8)	24.6 (22.2-26.7)	24.8 (22.8-27.7)
≤18.4	3 (4)	3 (4)	0
18.5-24.9	40 (47)	31 (46)	9 (50)
25.0-29.9	32 (38)	25 (37)	7 (39)
30.0-34.9	4 (5)	2 (3)	2 (11)
Unknown	6 (7)	6 (9)	0
Current or former smoker	62 (73)	45 (67)	17 (94)
Comorbidities			
None	9 (11)	8 (12)	1 (6)
Hypertension	52 (61)	41 (61)	11 (61)
Diabetes	32 (38)	23 (34)	9 (50)
Chronic lung disease [a]	18 (21)	13 (19)	5 (28)
Long-term oxygen therapy	0	0	0
Cardiovascular disease [b]	17 (20)	8 (12)	9 (50)
Chronic kidney disease	15 (18)	9 (9)	6 (33)
Hemodialysis	4 (5)	3 (4)	1 (6)
Immunodeficiency	8 (9)	5 (7)	3 (17)
Chronic liver disease	4 (5)	2 (3)	2 (11)
Malignancy	2 (2)	0	2 (11)
Dementia	2 (2)	1 (1)	1 (6)

Charlson comorbidity index	3 (2-4)	3 (2-4)	4 (3-6)
Clinical frailty scale	2 (1-3)	1 (1-3)	3 (1-3)
1-3 (non-frail)	72 (85)	58 (87)	14 (78)
4-7 (frail)	13 (15)	9 (13)	4 (22)
Barthel index, points	100 (100-100)	100 (100-100)	100 (100-100)
80-100 (independent)	79 (93)	64 (96)	15 (83)
60-79 (minimally dependent)	2 (2)	2 (3)	0
40-59 (partially dependent)	0	0	0
20-39 (very dependent)	1 (1)	0	1 (6)
<20 (totally dependent)	2 (2)	0	2 (11)
Unknown	1 (1)	1 (1)	0
Infection route			
Community acquired	71 (84)	59 (88)	12 (67)
Nursing facility acquired	1 (1)	1 (1)	0
Hospital acquired	13 (15)	7 (10)	6 (33)
Duration from onset of symptoms to hospital admission, days [c]	8 (6-9)	8 (6-10)	6 (3-8)
Duration from the onset of symptoms to ICU admission, days [c]	8 (6-10)	8 (6-11)	7 (5-8)

Data are presented as number (%) or median (interquartile range). ICU: intensive care unit. [a] Asthma, chronic obstructive pulmonary disease, interstitial lung disease, and/or bronchiectasis. [b] Coronary artery disease, arrhythmias, valvular heart disease, cardiomyopathy, and/or heart failure. [c] Data available for 81 patients.

Table 2 Clinical outcomes at hospital discharge in survivors

	Survivors (n = 67)	PMV cohort [a] (n = 23)	Non-PMV cohort (n = 44)	P-value
Disposition				
Discharged to home	35 (52)	3 (13)	32 (73)	<0.0001
Transferred to other hospital	32 (48)	20 (87)	12 (27)	
Duration of ICU stay, days	14 (9-29)	30 (23-40)	9 (7-13)	<0.0001
Duration of hospital stay, days	27 (17-53)	76 (56-95)	20 (15-27)	<0.0001
Duration of MV, days	9 (5-22)	31 (20-46)	6 (3-8)	<0.0001
Duration of hospital stay after liberation from MV, days	17 (10-36)	36 (27-53)	13 (9-21)	<0.0001

Data are presented as number (%) or median (interquartile range). PMV: prolonged mechanical ventilation, ICU: intensive care unit. [a] PMV was defined as >14 days of MV.

Table 3 Organ dysfunction and respiratory symptoms at hospital discharge in survivors

	Survivors (n = 67)	PMV cohort (n = 23)	Non-PMV cohort (n = 44)	P-value
SOFA score	1 (0-2)	1 (1-2)	1 (0-1)	0.07
Need for respiratory support				
No respiratory support	59 (88)	17 (74)	42 (95)	<0.01
Oxygen by mask or nasal prongs	7 (10)	5 (22)	2 (5)	
Oxygen by noninvasive ventilation or High-flow nasal cannula oxygen therapy	0	0	0	
MV	1 (1)	1 (4)	0	
Tracheostomized	17 (25)	17 (74)	0	<0.0001
Renal replacement therapy [a]	4 (6)	3 (13)	1 (2)	0.08
Respiratory symptoms				
Dyspnea on exertion	50 (75)	22/22 (100)	28/44 (64)	<0.0001
Dyspnea at rest	1 (1)	0/22	1/44 (2)	0.48
Cough	4 (6)	1/22 (4)	3/44 (7)	0.69
Chest pain	0	0/22	0/44	

Data are presented as number (%), number/total number (%), or median (interquartile range). PMV: prolonged mechanical ventilation, SOFA: sequential organ failure assessment. [a] Including three patients treated with hemodialysis prior to COVID-19 infection.

Table 4 Functional status at hospital discharge in survivors

	Survivors (n = 67)	PMV cohort (n = 23)	Non-PMV cohort (n = 44)	P-value
Barthel index	90 (45-100)	35 (5-65)	100 (85-100)	<0.0001
80-100 (independent)	40 (60)	3 (13)	37 (84)	
60-79 (minimally dependent)	7 (10)	5 (22)	2 (5)	
40-59 (partially dependent)	5 (7)	1 (4)	4 (9)	
20-39 (very dependent)	7 (10)	6 (26)	1 (2)	
<20 (totally dependent)	8 (12)	8 (35)	0	
Intensive care unit mobility scale	10 (9-10)	9 (5-9)	10 (10-10)	<0.0001
9-10 (walking independently)	57 (85)	14 (61)	43 (98)	
7-8 (walking with assistance)	2 (3)	1 (4)	1 (2)	
2-6 (out-of-bed activity)	7 (10)	7 (30)	0	
1 (in-bed activity)	0	0	0	
0 (noting in bed)	1 (1)	1 (4)	0	
Functional oral intake scale	7 (5-7)	3 (1-7)	7 (7-7)	<0.0001
4-7 (total oral diet)	54 (81)	10 (43)	44 (100)	
2-3 (tube dependent with oral intake)	5 (7)	5 (22)	0	
1 (nothing by mouth)	8 (12)	8 (35)	0	
Medical Research Council sum score [a]	54 (46-60)	44 (36-51)	58 (49-60)	<0.0001
Muscle weakness	18/64 (28)	16/23 (70)	2/41 (5)	
HADS [b]				
HADS-A	5 (3-8)	9 (6-11)	5 (2-7)	<0.01
Anxiety (HADS-A >7)	18/54 (33)	9/15 (60)	9/39 (23)	
HADS-D	6 (3-8)	7 (6-10)	4 (3-8)	<0.01
Depression (HADS-D >7)	17/54 (31)	7/15 (47)	10/39 (26)	
Cognitive impairment [c, d]	13/55 (24)	5/15 (33)	8/40 (20)	0.30

Data are presented as number (%), number/total number (%), or median (interquartile range). PMV: prolonged mechanical ventilation, HADS: Hospital anxiety and depression scale. [a] Data available for 64 survivors [b] Data available for 54 survivors [c] Cognitive impairment was defined as Mini-Cog score <3 and/or Mini-Mental State Examination score <24. [d] Data available for 55 survivors.

Figure 1.

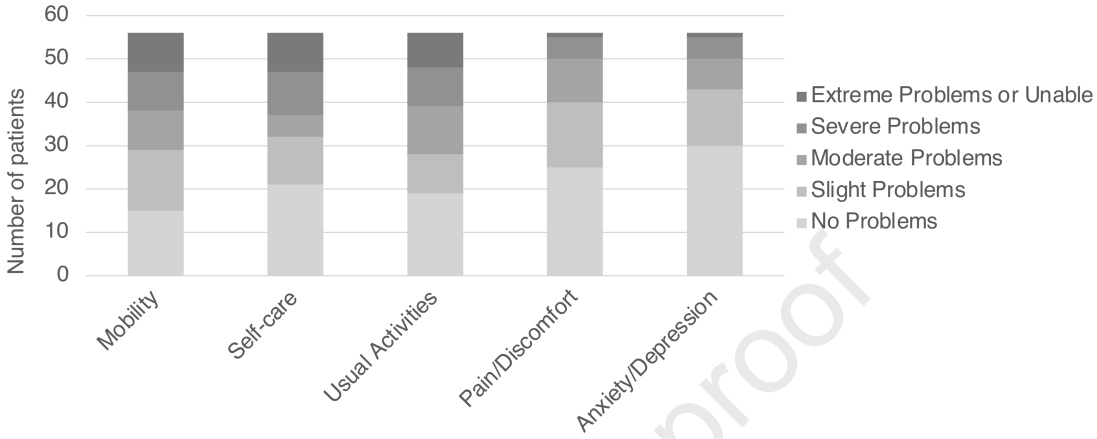

Figure 2.